

HIV-2 and Natural Protection Against HIV-1 Infection

Karin Travers *et al.* report that infection with HIV-2, an apparently less virulent strain of the human immunodeficiency virus (HIV), provided natural protection, estimated at approximately 70%, against infection with HIV-1 in a cohort of female sex workers in Senegal (1). This finding rests on the significantly lower HIV-1 incidence rate over a 9-year period among HIV-2-infected women [1.06 per 100 person-years of observation (PYO) in tables 1 and 2 of the report (1)] than among HIV-seronegative women [shown as 2.53 per 100 PYO in table 1 but 2.45 per 100 PYO in table 2 of the report (1)]. However, in a 1994 paper (2) the same research group reported an HIV-1 incidence rate of 1.11 per 100 PYO in the same general population of HIV-seronegative female sex workers followed over roughly the same period. Had the HIV-1 incidence rate among seronegative women in the 1995 report (1) been similar to that reported the year before, no reduced HIV-1 incidence would have been found among HIV-2-infected women relative to uninfected women, and therefore there would have been no suggestion of natural protection.

A comparison of the data from these two papers (1, 2) (Table 1) shows that, while the numbers of women seroconverting annually in the two studies were identical through 1989 and similar in 1990 and 1991 (differences in 1992 and 1993 were presumably due to the longer follow-up period in the later paper), the 1995 report (1) includes only about half as many seronegative women (618 women contributing 2410 PYO) as reported in the earlier paper (2) (1277 women contributing 4141 PYO). The 1994 paper (2) appears to report on all

initially HIV-seronegative female sex workers enrolled in the Dakar study clinic. The time observed before their latest serologic test served as the denominator, while the number of seroconversions in the group was the numerator for computing the HIV-1 incidence rate. The 1995 report (1) followed only a subset of the earlier study population, limited to those women with HIV-1 or HIV-2 infection (apparently including both initially prevalent cases and cases incident during follow-up) along with two randomly selected seronegative women for each infected woman, matched on the basis of age, nationality, and number of years of registered prostitution. This procedure seems to have reduced the number of seronegative women followed up (and the corresponding PYO) by a factor of about two, yet included virtually all the seronegative women who became HIV-1 positive. It seems highly unlikely to us that truly random sampling would have brought all the seroconverters into the smaller group, and a selection bias favoring seroincident HIV-1 cases may have occurred. Such a bias would artifactually elevate the HIV-1 incidence rate in the seronegative group, giving by comparison the appearance of a lower HIV-1 incidence in the HIV-2 group.

Because of this uncertainty, the evidence is currently insufficient to suggest that HIV-2 infection protects against HIV-1. We hope Travers *et al.* will clarify how virtually all the seroconverters from the larger study population were selected into their seronegative comparison group. To minimize the effect of potential selection biases, we would encourage the authors to recalculate the HIV-1 incidence rates in their unique and valuable study population

using a retrospective cohort analysis, analogous to evaluating vaccine efficacy. For this recalculation, the HIV-2 cohort would remain the 187 women with prevalent or incident HIV-2 infection. The comparison cohort, however, should be limited to those 374 women who, while still seronegative, were matched 2-for-1 to the HIV-2 cases, rather than the 618 women that were used. Such a recalculation could determine whether in fact HIV-1 incidence was influenced by pre-existing HIV-2 infection and therefore whether any natural protection may have occurred.

Alan E. Greenberg

Stefan Z. Wiktor

Projet RETRO-CI,

Abidjan, Cote d'Ivoire

Kevin M. DeCock

Peter Smith

London School of Hygiene and

Tropical Medicine,

London WC1E 7HT, United Kingdom

Harold W. Jaffe

Timothy J. Dondero, Jr.*

Centers for Disease Control and Prevention,

Atlanta, GA 30333, USA

*E-mail: tjd@cidhiv1.em.cdc.gov

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2. P. J. Kanki *et al.*, *Lancet* **343**, 943 (1994).

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Response: Greenberg *et al.* incorrectly assume that data excerpted from our comparative HIV incidence study published in 1994 in *Lancet* (1) can be directly compared with excerpted data from our 1995 report in *Science*, which evaluated HIV-2 protection (2). The protective effect of HIV-2 cannot be assessed with the use of crude incidence estimates. The baseline risk for HIV-1 infection must be comparable between the HIV-negative and HIV-2-positive groups, and this was accounted for in our study design and analysis (2). Further, these two studies (1, 2) were distinct in the research questions that each addressed, criteria for subject enrollment, and follow-up and analysis. The HIV-2 protection study (2) population was composed of registered sex workers; some of these women represented a subset of the study population described in *Lancet* (1), but there are three important differences between the two studies. First, HIV-positive individuals were eligible for enrollment in the HIV-2 protection study (2), while the *Lancet* study (1) excluded them. (Each enrolled HIV-positive woman was further matched to two HIV-negative women to achieve comparable data with regard to follow-up and baseline risk for

Table 1. Comparison of data about HIV-1 infection from two studies of the same basic population followed over roughly the same period. PYO, person-years of observation. IR, incidence rate.

Sample Year	Travers <i>et al.</i> (1)			Kanki <i>et al.</i> (2)		
	Sero-converters	PYO	IR	Sero-converters	PYO	IR
1985	0	110	0	0	187	0
1986	0	229	0	0	448	0
1987	4	284	1.41	4	552	0.72
1988	4	307	1.30	4	609	0.66
1989	5	337	1.48	5	704	0.71
1990	10	350	2.86	9	732	1.23
1991	19	313	6.06	18	640	2.81
1992	13	274	4.74	6	274	2.19
1993	6	206	2.92			
Totals	61	2410	2.53	46	4141	1.11

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Alan E. Greenberg, Stefan Z. Wiktor, Kevin M. DeCock, Peter Smith, Harold W. Jaffe and Timothy J. Dondero Jr.

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